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Local causes of LEG OEDEMA

inside

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Background

LEG oedema, or swelling of the legs, is common and often presents a difficult diagnostic dilemma because of the diverse nature of its possible causes. Patients seek medical advice for a variety of reasons, including pain and inability to walk.

The distribution of oedema is an important guide to the underlying cause. The most important initial question is whether the oedema is localised or generalised. Leg oedema may be either unilateral or bilateral. Bilateral swelling is more commonly due to systemic conditions whereas unilateral swelling more often represents local pathology.

Table 1 lists the most common causes of leg oedema that present to GPs today. Local causes are usually related to venous or lymphatic disease. Systemic causes include heart, liver and kidney dysfunction.

Management is based on the underlying cause, so an accurate and timely diagnosis is paramount. Investigations should be directed to the postulated aetiology but should also be geared to excluding other possibilities. This article discusses the management of common local causes of leg oedema.

Table 1: Causes of leg oedema

Systemic
- Cardiac dysfunction:
  - left ventricular systolic impairment: ischaemic heart disease, valvular disease
  - left ventricular diastolic dysfunction: hypertension
  - right ventricular dysfunction (pericardial effusion, chronic cardiac failure, end-stage chronic airflow limitation)
- Fluid overload
- Renal disease:
  - acute renal failure (eg, acute glomerulopnephritis)
  - chronic renal failure
- Hypoproteinaemic states:
  - chronic liver disease
  - nephrotic syndrome
  - malnutrition
  - protein-losing enteropathy
  - malabsorption
- Endocrine:
  - hypothyroidism
  - Cushing's syndrome
- Drugs:
  - calcium-channel antagonists
  - corticosteroids
  - NSAIDs
  - oestrogens
- Anaemia
- Others:
  - hereditary angioneurotic oedema
  - pregnancy
  - idiopathic

Local
- Venous:
  - acute DVT
  - post-thrombotic sequelae (eg, venous incompetence, venous hypertension)
  - varicose veins
  - obstruction to venous return (eg, pregnancy, pelvic tumours, inferior vena cava obstruction)
- Lymphatic:
  - primary lymphoedema
  - secondary lymphoedema
- Stasis:
  - paralysis
  - poor mobility
  - obesity
- Inflammation:
  - cellulitis
  - allergic reactions
- Trauma
- Congenital:
  - arteriovenous malformations

Deep venous thrombosis

DEEP venous thrombosis (DVT) is a prominent cause of lower limb swelling. It tends to be unilateral and the extent, site and number of previous episodes will determine the degree of swelling. DVT can cause two clinical scenarios: acute DVT and post-thrombotic syndrome (PTS).

Risk factors

There are many independent risk factors for DVT and pulmonary embolism (PE); however, it is not until there is a combination of these that a DVT will occur. Risk factors include:

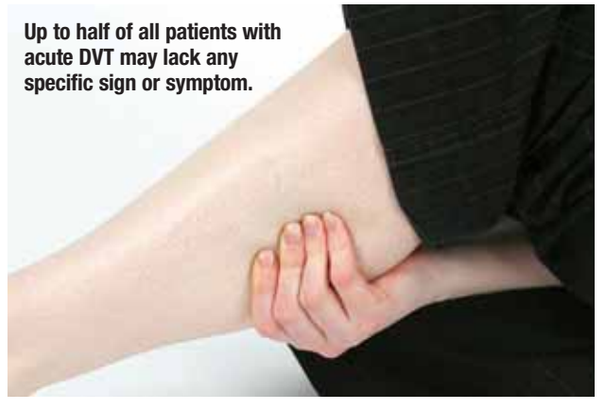
- Increasing age.
- Male gender.
- Surgery or trauma.
- Hospital or nursing home confinement.
- Malignancy.
- Neurological disease with extremity paresis.
- Central venous catheter or transvenous pacemaker.
- Prior superficial vein thrombosis.
- Varicose veins.

Pregnancy, oral contraceptives and HRT can all increase the risk for women. The relative risk increases progressively from 2.4 in those with one risk factor to more than 20 among those with three or more risk factors.

Independent predictors for recurrent DVT, which occurs within 10 years in up to 30% of cases, include increasing age, obesity, malignancy and extremity paresis.

Acute DVT

Venous obstruction is the cause of symptoms and signs in the acute setting. Signs and symptoms vary with the extent of the venous tree involved and include:



Up to half of all patients with acute DVT may lack any specific sign or symptom.

- Pain.
- Oedema.
- Erythema.
- Tenderness.
- Fever.
- Prominent superficial veins.
- Calf pain on passive dorsiflexion of the foot (Homans' sign).
- Peripheral cyanosis.

However, these may not always be present or obvious and a high index of clinical suspicion should always be maintained.

Complete thrombus resolution has been reported in 56% of patients monitored for nine months.[1] However, recanalisation may continue, albeit at a slower rate, for months to years after the acute event.

Among patients with proximal DVT, recurrent thromboembolic events have been reported in 5.2% of patients treated for three months with standard anticoagulation measures, compared with 47% of patients who were inadequately treated with low-dose subcutaneous heparin.[2]

Proximal propagation may also complicate isolated calf vein thrombosis in up to 23-30% of untreated patients. Left untreated, calf vein thrombosis will extend into proximal veins in 25-33% of cases.[3,4]

The important complications of DVT are PE and PTS. Inadequate treatment of proximal lower-extremity venous thrombosis is associated with a 20-50% risk of clinically significant PE; however, most PE is clinically silent. High-probability lung scan results may be obtained in 25-51% of patients with documented (treated) DVT in the absence of pulmonary symptoms.

The post-thrombotic syndrome

PTS is the residual effect in the limb from the venous hypertension caused by residual obstruction and resultant incompetence from the destruction of venous valves. It typically occurs at least 10 years after the initial episode of DVT.

The symptoms of pain, oedema, hyperpigmentation and/or ulceration are typical of PTS, which occurs in 29-79% of patients with a history of DVT. There is no clear relationship between the extent of thrombus or symptoms on initial presentation and ultimate clinical outcome.

Studies have found that the risk factors for PTS appear to be ipsilateral recurrence of DVT, poor quality of initial anticoagulation for the treatment of DVT, and increased BMI. Factors that reduce the risk of development of PTS are early thrombolysis, early effective anticoagulation and the long-term wearing of graduated calf-compression stockings.

Investigations

Unfortunately, the diagnosis of DVT based on clinical signs and symptoms alone is inaccurate; in up to half of patients with classic clinical findings, a DVT is not confirmed by diagnostic testing. Furthermore, up to half of all patients with acute DVT may lack any specific sign or symptom.

Contrast venography has historically been the gold standard for diagnosing acute DVT. However, venography is inconvenient, expensive and may cause significant discomfort.

Duplex ultrasonography is now the most widely used non-invasive tool for diagnosing DVT. Evaluating the lower extremities includes assessing venous compressibility, intraluminal echoes, venous flow characteristics and luminal colour filling. Despite its usefulness, there are limitations, especially in adequately visualising the iliac veins, and there may be considerable operator variability.

CT venography may be used as a second-line investigation or when an experienced vascular laboratory is unavailable. It is also helpful to identify iliac vein and inferior vena cava thrombosis.

D-dimer assays can be useful in diagnosis in certain situations. D-dimers are products of the degradation of cross-linked fibrin by plasmin. When measured by ELISA, sensitivity for the diagnosis of DVT is as high as 96.8%. Unfortunately, these measurements are also quite non-specific (as low as 35.2%) with a high false-positive rate associated with:

- Disseminated intravascular coagulation.
- Malignancy.
- Postoperative states.
- Pre-eclampsia.
- Infection.
- Recent trauma.

The high sensitivity of D-dimer measurements makes it theoretically possible to exclude a diagnosis of DVT on the basis of a negative result, as long as the patient is in a low-risk group (ie, outpatients with no previous DVT, no PE symptoms).

Patients with recurrent DVT or DVTs involving more than the tibial vessels should be evaluated for a thrombophilia.

Anticoagulant therapy for venous thromboembolism

The objectives of treatment in patients with venous thromboembolism (VTE) are to prevent death from PE, prevent recurrent VTE and prevent PTS.

The accepted anticoagulant therapy for VTE is either continuous IV heparin or subcutaneous (SC) enoxaparin (Clexane) then changing to oral warfarin. Heparin or enoxaparin is continued until the INR has been within the therapeutic range (2.0-3.0) for two consecutive days.

Calf vein thrombosis

Isolated calf vein thrombi are usually considered relatively low risk for causing PE. However, this risk is not nil, and proximal propagation (occurring in up to 30% of patients) significantly increases the risk for PE and PTS.

Debate still exists on whether to anticoagulate these patients; however, patients with a calf DVT have been shown to benefit from 6-12 weeks of anticoagulation. If anticoagulation is not given, an antiplatelet agent such as low-dose aspirin (100mg daily) should be started and graduated compression stockings used. A repeat venous duplex scan should be ordered within 5-7 days to determine progression.

Femoropopliteal venous thrombosis

Anticoagulation is standard therapy but does not dissolve the thrombi. Under circumstances of effective anticoagulation, natural fibrinolysis may at least partially recanalise occluded veins. Even without recanalisation, morbidity may be minimal if thrombosis is limited to the femoral vein in the thigh. This treatment can be for 3-6 months, depending on the patient's risk.

Iliofemoral thrombosis (proximal thrombosis)

Patients with proximal thrombosis are usually symptomatic. Characteristically these patients have thigh and calf oedema and pain on both rest and ambulation. PE from these large veins may be fatal.

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These patients need immediate anticoagulation with IV heparin, followed by warfarin for at least 12 months.

The young physically active patient with proximal venous thrombosis should be considered for catheter-based thrombolytic therapy followed by anticoagulation to lessen the long-term morbidity of DVT. It has been demonstrated that early clot clearance by either thrombectomy or catheter-directed thrombolysis has better long-term outcomes than anticoagulation alone.

Long-term treatment of VTE

In addition to local management, patients with recurrent VTE or continuing risk factors such as cancer, antithrombin deficiency or the antiphospholipid syndrome should be treated indefinitely with warfarin (unless contraindicated).

Patients with activated protein C resistance (factor V Leiden mutation) should probably receive indefinite treatment if they have recurrent disease, are homozygous for the gene or have multiple thrombophilic conditions.

Inferior vena caval filters

Vena caval filters are metal devices that are placed in the inferior vena cava under fluoroscopic guidance. These devices are designed to 'catch' life-threatening emboli in the inferior vena cava. The devices can be permanent or temporary, depending on the indication.

The main indications for vena caval filters are contraindications to anticoagulants (including complications of anticoagulation that have mandated therapy be discontinued), recurrent PE despite adequate anticoagulation, and for prophylactic placement in high-risk patients (table 2).

Prophylaxis in air travel

The risk of DVT in air travel is in fact very low — one in one million in short flights, increasing to one in 70,000 for journeys longer than 12 hours.

There is a higher risk of DVT in patients with previous DVT or PE, pro-thrombotic states, recent surgery or significant medical illness. These patients should use both graduated compression stockings and SC enoxaparin or heparin. For all other patients, advice should be to:

Table 2: Indications for insertion of a vena caval filter

Absolute indications
- Deep venous thrombosis or documented thromboembolism in a patient with a contraindication to anticoagulation
- Complications of anticoagulation that have forced therapy to be discontinued
- Recurrent pulmonary embolism despite adequate anticoagulation
- Prophylactic placement in high-risk patients

Relative indications
- Demonstrated free-floating iliofemoral thrombus
- A propagating iliofemoral thrombus despite adequate anticoagulation
- Septic pulmonary embolism
- Chronic pulmonary embolism in a patient with pulmonary hypertension and cor pulmonale
- A patient with >50% occlusion of the pulmonary vascular bed and who would not tolerate any additional thrombus
- Severe ataxia and risk of falling

- Ensure adequate hydration.
- Mobilise before, during and after the flight.
- Avoid combining sedatives with excess alcohol.
- Wear non-restrictive clothing.

Treatment of oedema caused by DVT

Lower-limb oedema can be treated in the acute DVT setting with graduated compression stockings and appropriate treatment of the DVT with anticoagulants. The acute swelling tends to settle over 1-2 months, and use of graduated compression stockings should be continued until the thrombus load has been documented as almost resolved. This reduces the risk of developing PTS later in life.

Venous insufficiency

Pathophysiology

BETWEEN 10% and 35% of adults have some form of chronic venous disorder, ranging from spider veins and simple varicosities to venous ulcers, the last of which affect 4% of people aged over 65.

Venous reflux is seen when valvular destruction or dysfunction occurs. Valvular reflux causes a rise in ambulatory venous pressure and a cascade of pathological events that manifest clinically as:
- Varicose veins.
- Lower extremity oedema.
- Pain.
- Itching.
- Skin discolouration.
- Venous ulceration (in the most severe form).

Symptoms and signs specific to abnormal venous function arise from chronic ambulatory venous hypertension, and are known as chronic venous insufficiency (CVI). CVI is now thought of as a disease of chronic inflammation due to a sustained injury secondary to venous hypertension.

The primary injury is extravasation of macromolecules and erythrocytes into the dermal interstitium. Erythrocyte degradation products and interstitial proteins are potent chemoattractants and presumably represent the inflammatory signal responsible for leucocyte recruitment.

Causes of persistent venous hypertension are:
- Primary valvular incompetence of the macrocirculation veins.
- Secondary valvular incompetence due to valve destruction in PTS.
- Chronic venous obstruction due to previous DVT.

Investigation of CVI

The clinical history should include questions about:
- Pain or discomfort.
- Visible veins.
- Itch.
- Skin pigmentation.
- Ulceration.
- Bleeding from superficial veins.
- Whether the swelling is unilateral or bilateral, and if it worsens during the day.
- Family history.
- Previous DVTs.

The examination begins with observation of each limb in both the supine and standing positions. The distributions of visible large and small venous tributaries are noted. When standing, the long and short saphenous veins are palpated, and tested for a cough impulse, suggesting stress incompetence. Pigmentation (especially lipodermatosclerosis), oedema, induration, cellulitis, lymphangitis or ulceration should be noted.

Failure to consider other medical illnesses and differential diagnoses (table 3) may result in serious misdiagnosis (malignancy), frequent recurrence (ulcerative colitis or collagen vascular disease) and non-healing (obesity).

It must be noted that venous ulcers can transform into malignant ulcers — either squamous cell carcinoma or basal cell carcinoma. Suggestions of malignancy include raised edges, an irregular appearance, bleeding and prolonged failure to heal. Malignancies can be easily diagnosed through biopsy with local anaesthesia.

Table 3: Differential diagnosis of chronic venous ulcers*
- Arterial disease
- Mixed arterial and venous disease
- Arteriovenous shunting
- Peripheral neuropathies
- Malignancies
- Blood dyscrasias
- Vasculitides
- Metabolic diseases: gout, myxoedema
- Chronic infectious diseases: osteomyelitis, TB, leprosy, syphilis
- Tropical ulcer

*Source: Padberg 2005[5]

Investigation of CVI should include a venous duplex scan of the deep, superficial and perforating veins. The examination identifies patency, competency and whether there is normal venous anatomy. This information linked with the clinical symptoms helps direct therapeutic options.

Invasive investigations such as venography or ambulatory venous pressures may be (rarely) requested when the findings of clinical and non-invasive examinations are insufficient to provide complete diagnosis or as a part of a therapeutic endeavour such as thrombolysis and stenting.

Non-operative treatment of CVI

Elevation of the lower extremities, with the feet above the thighs when sitting and above the heart when supine, is almost completely accepted as effective treatment for venous ulceration. However, it is impractical for most patients as anything but a short-term solution to a refractory or enlarging ulcer.

Compression therapy

Compression therapy remains the primary treatment for CVI. It promotes fluid resorption and resolution of oedema, with improved diffusion of nutrients to the skin and subcutaneous tissues.

Provided there is no cellulitis, patients are usually fitted with below-knee, grade-2 graduated compression stockings. Patients should obtain two pairs to allow laundering, and wear the stockings at all times while ambulatory and remove them at bedtime.

Wound care of ulcers can still occur under the compression bandage or stocking. After the ulcer has healed, the patient is instructed to continue ambulatory compression therapy indefinitely. Failure to comply with perpetual compression therapy increases the ulcer recurrence rate from about 20% to 60-100%.

The most difficult problem is poor patient compliance, due to discomfort in warm weather, or because some patients have hypersensitive skin in the lipodermatosclerotic area adjacent to the ulcer or at the site of a previously healed ulcer. When beginning therapy, patients should be instructed to wear elastic compression stockings for only as long as tolerable (perhaps only 10-15 minutes at first) and to gradually lengthen this time. Occasionally, patients may initially need to be fitted with stockings of a lesser degree of compression.

Another frequent problem is the difficulty many weak, elderly, or arthritic patients experience applying the stockings. Commercially available devices can assist these patients, such as silk or plastic inner sleeves, or wire-frame devices.

Arterial disease should also be considered before proceeding with compression therapy, as this may aggravate the ulcer or cause further lower-limb ischaemia. This may be done by performing an ankle brachial index or, if concerned, arranging further assessment by a vascular specialist.

Pharmacological therapy

Despite the oedema, diuretics have no role in the treatment of CVI.

Zinc has been found to be of benefit in the healing of venous ulcers, but only if pre-treatment zinc levels are low, and not in all studies.

Oxpentifylline (Trental 400) reduces blood viscosity, white blood cell adhesiveness and neutrophil activation and degranulation. In a meta-analysis, oxpentifylline in combination with compression therapy was more effective than placebo and compression in complete ulcer healing.[6,7]

Aspirin 300mg/day has also been show to speed ulcer healing, most likely due to its anti-inflammatory and antiplatelet effects.

Topical antibiotics have been advocated as a treatment of venous ulceration for many years. However, unless an ulcer is actively infected, topical or systematic antibiotics are unnecessary, as bacterial colonisation of ulcers has little impact on healing.

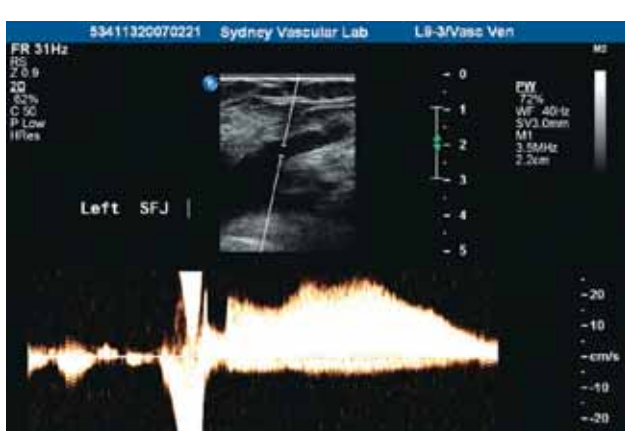
Varicose veins

VARICOSE veins, or superficial venous incompetence, can lead to CVI. Patients with lower-limb oedema and superficial venous incompetence can be treated by surgical or endovenous laser therapies.

Pathophysiology and clinical features

When the valves of the perforator veins become incompetent they permit abnormally high pulses of hydrodynamic pressure to be transmitted from the deep system to the relatively unsupported superficial veins. The best-recognised connections between the superficial and the deep venous systems are the saphenofemoral and saphenopopliteal junctions. Incompetence of the check valves at their termination causes increased hydrostatic pressure on the more distal veins, venous dilation and further venous incompetence, in a progressive fashion. When the hydrostatic forces of gravitational reflux are added to the hydrodynamic forces of muscular contraction, they produce localised blowouts, or varicosities.

Varicose veins, telangiectatic blemishes, and dilated, tortuous, flat, blue-



Ultrasound demonstrating incompetence at the saphenofemoral junction (significant being greater than 0.5 seconds duration of reflux).

green reticular veins are not normal physical findings. They are evidence of venous dysfunction. Telangiectasias are defined as a confluence of permanently dilated intradermal venules of <1mm in diameter. Reticular veins are defined as permanently dilated, bluish intradermal veins, usually 1mm to <3mm in diameter.

Longstanding venous dysfunction causes marked skin changes, from woodiness and fibrosis to lipodermatosclerosis (from haemosiderin deposition) and atrophie blanche (a confluence of scarring from multiple episodes of skin breakdown and poor healing occuring in severe disease).

The aching pain is related to pressure of the dilated vessels on a network of somatic nerve fibres in adjacent subcutaneous tissues and the oedema caused by a fluid shift from venous to interstitial compartments by venous hypertension.

Treatment

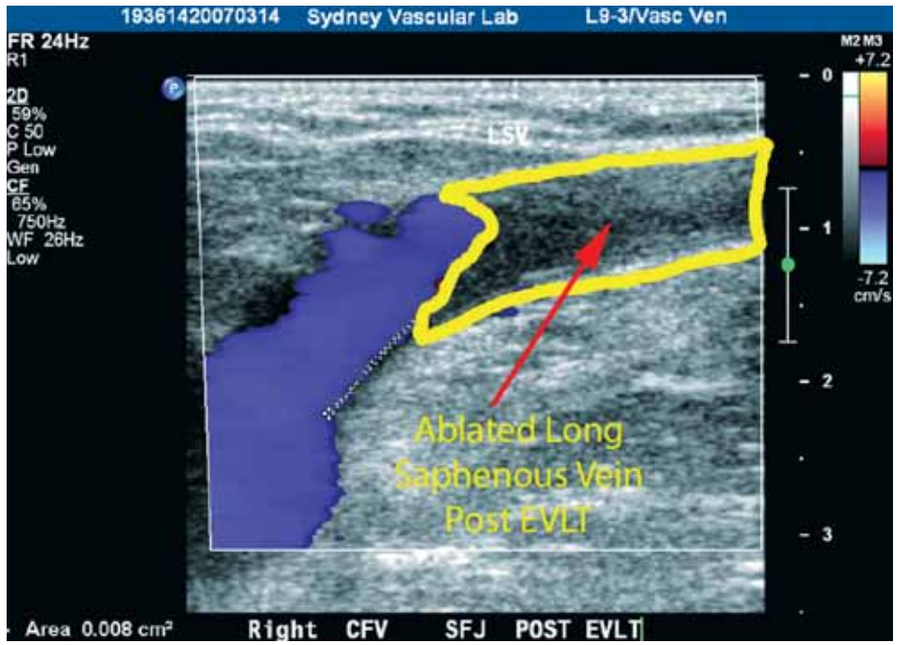
Extensive availability of duplex ultrasonography has revealed another reason for intervening in varicose veins, in addition to those listed in table 4 — deep venous function is improved by superficial venous surgery.

Doppler evaluation and duplex scanning have shown that saphenofemoral junction reflux is present in 70% of symptomatic limbs selected for surgery. In such limbs the saphenous vein at the femoral junction must be treated. About 15% of patients are found to have short saphenous vein incompetence, which requires flush ligation and removal of some of the vein.

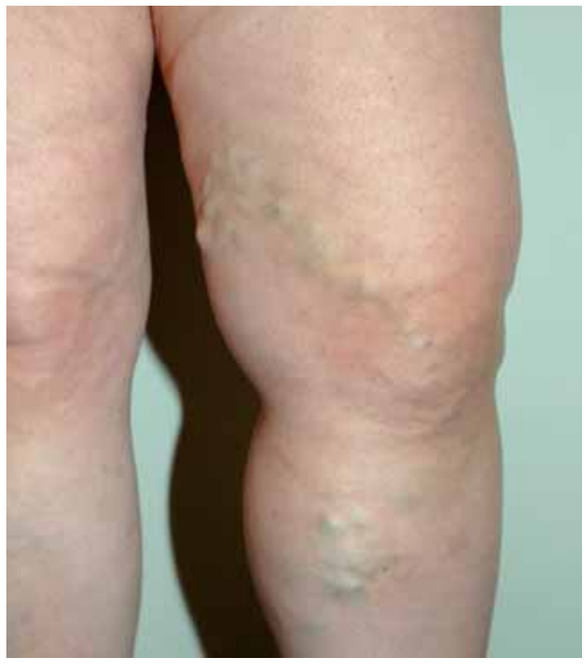
Table 4: Varicose veins: indications for intervention*

■ Venous ulceration
■ Pain and aching
■ Swelling secondary to superficial venous hypertension
■ Bleeding
■ Superficial thrombophlebitis
■ Cosmetic

*Source: Bergan 2005[8]



An ablated long saphenous vein after endovascular laser treatment (lack of blue demonstrates no blood flow in that area).



Varicose veins can lead to chronic venous insufficiency.

Surgical removal of the long saphenous vein is now performed by the stripping or laser ablation of the vein from the groin to the knee. Supplement avulsions or sclerotherapy are used to remove other clusters of varicose veins. Sclerotherapy without addressing the saphenofemoral or saphenopopliteal reflux will fail.

Recent developments in treatment of the long saphenous vein have focused on attempting to minimise postoperative discomfort while maintaining the benefits of saphenous vein ablation. Endovascular laser treatment can be performed using local anaesthesia only, without a groin incision. It causes rapid thermal electrocoagulation of the vein wall and its valves, which in turn causes total loss of vessel wall architecture, disintegration and carbonisation.

There is now level I evidence indicating that such treatment is beneficial.[9] At 1-3 years, reported results from ablation of the saphenous vein are as good as those from conventional surgical treatment, and clinical observations suggest that patients are much more comfortable after saphenous ablation than after stripping.

Surgical treatment of chronic occlusions of the iliac veins and the inferior vena cava

Apart from DVTs, venous occlusion may also develop because of trauma or irradiation, or as a result of external compression of deep veins by:

- Retroperitoneal fibrosis.
- Tumours.
- Cysts.
- Aneurysms.
- Abnormally inserted muscle (popliteal vein entrapment).
- Fibrous bands or ligaments (soleal arch syndrome, femoral vein compression by the inguinal ligament).

May-Thurner syndrome (compression of the left common iliac vein by the overriding right common iliac artery) is a rare but frequently overlooked cause of left iliofemoral venous thrombosis.

The approach to any of the above causes of proximal venous occlusion is to consider endovascular techniques first, as the advances being made in this field are significantly decreasing the number of patients requiring open surgical reconstruction. Endovascular techniques involve relatively low-risk angioplasty and stenting to reopen a stenosed or occluded segment, whereas the open techniques of vein or synthetic grafting bypass the affected vein.

Lymphoedema

THE lymphatic vasculature consists of initial lymphatics, the lymphatic pre-collectors, lymphatic ducts and lymph nodes. The superficial system collects lymph from the skin and subcutaneous tissue and the deeper system drains subfascial structures.

When lymphatic vessels are absent, underdeveloped or obstructed, lymphatic flow from the extremities is impeded and lymph accumulates. The resultant clinical presentation, lymphoedema, can affect any part of the body but tends to target the arms and legs. About 300,000 Australians have lymphoedema at any given time.

Classification

The simplest classification requires differentiation between primary and secondary causes. Impedence to lymphatic flow may be due to an inborn defect (primary) or an acquired loss of lymphatic patency (secondary) (table 5).

Primary lymphoedema

Primary lymphoedema can be classified either according to the age of the patient when the oedema first appears, or by its lymphangiographic appearance.

Patterns of lymphatic dysfunction

There are four patterns of lymphatic dysfunction:

- Hypoplasia (or obstruction) of lymphatics distal to the inguinal nodes.
- Obstruction of pelvic vessels, with or without obliteration of distal vessels.
- Hyperplasia of lymphatic vessels.
- Incompetent, dilated lymphatic channels (megalymphatics).

About one-third of cases are related to aplasia (absence of lymphatic trunks), hypoplasia (reduced number or calibre of lymphatic channels) or obstruction of the distal lymphatics, with relatively normal proximal vessels. Swelling is usually bilateral and mild and women are affected more frequently. The prognosis is good; after the first year of symptoms there is little extension in the same limb or to uninvolved extremities. However, in about 40% of patients, affected limb girth continues to increase gradually.

In more than 50% of cases the defect primarily involves obstruction of the proximal lymphatics or nodes. There is possibly a slight female predominance. Swelling tends to be unilateral and severe, and the extent and degree is more likely to progress, with subsequent involvement of the distal lymphatics.

A minority of patients have bilateral hyperplasia of the lymphatics or tortuous dilated incompetent lymphatics (megalymphatics), with a male predominance. There is primary lymphatic valvular incompetence and an increased number of lymphatic channels, with varicosities of the major collecting vessels. Megalymphatics are associated with a greater extent of involvement and a worse prognosis.

Table 5: Classification of lymphoedema

Primary lymphoedema

- Congenital lymphoedema:
  - autosomal dominant: familial (Milroy's disease, lymphoedema-distichiasis syndrome)
  - autosomal recessive: syndrome associated
  - sporadic
- Lymphoedema praecox:
  - familial (Meige disease)
  - sporadic
- Lymphoedema tarda

Secondary lymphoedema

- Post-surgical — lymph node dissection, vascular surgery
- Neoplastic — intrinsic or extrinsic obstruction
- Parasitic — filariasis
- Post-infectious
- Post-traumatic
- Complicating chronic venous insufficiency

Table 6: Differential diagnosis of lymphoedema

- Chronic venous insufficiency
- Post-phlebitic syndrome
- Reflex sympathetic dystrophy
- Myxoedema
- Lipoedema
- Malignant lymphoedema

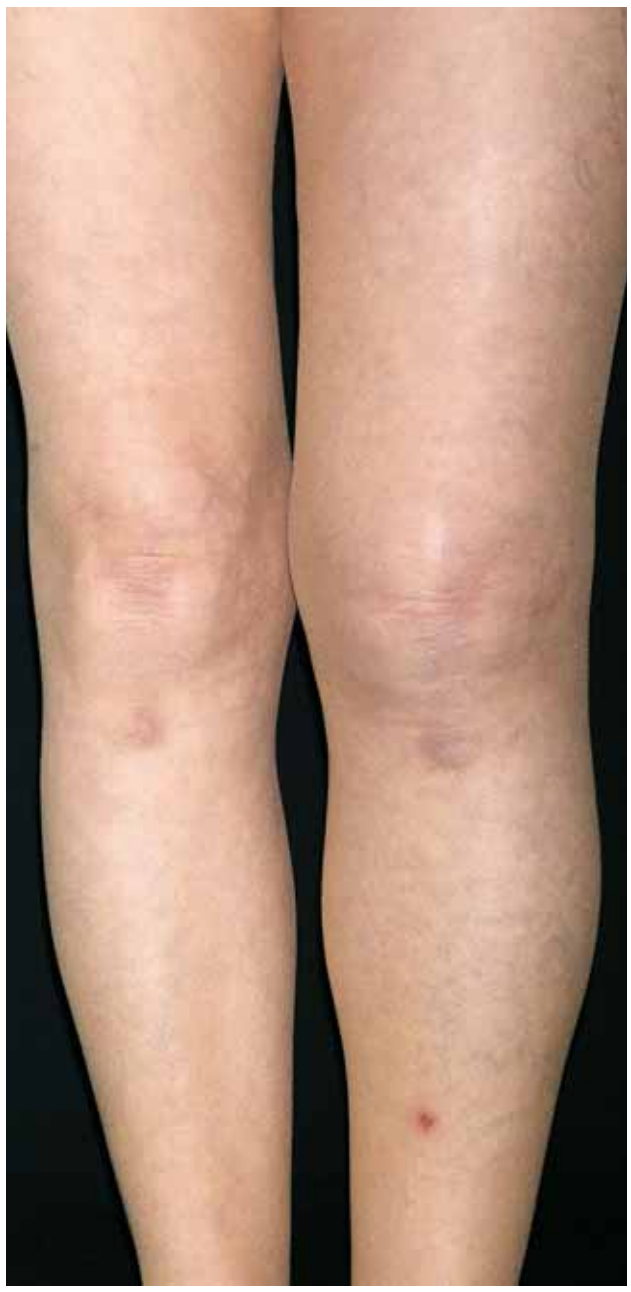
Age of first appearance

Congenital lymphoedema is apparent at birth or becomes recognised during the first two years of life. It represents about 15% of primary lymphoedema cases. There is typically aplasia or hypoplasia of lymphatic structures. In rare cases involvement of multiple limbs, genitalia or facial structures may be seen.

Lymphoedema praecox is most commonly first detected at puberty but its appearance may be delayed until the third decade. It comprises about 75% of cases and is typified by a hypolastic lymphangiographic pattern, usually beginning with foot and ankle swelling.

Lymphoedema tarda typically manifests after age 35-40. The lymphatic channels may be hypoplastic or hyperplastic.

A family history is evident in a minority of cases. The congenital autosomal dominant form is known as Milroy's disease. The term Meige disease is applied to the praecox familial form, also autosomal dominant. Autosomal recessive forms can sometimes occur.



Lymphoedema manifesting with sudden onset of swelling of one whole leg suggests proximal obstruction, and secondary causes such as a tumour must be excluded.

Primary lymphoedema is also associated with Turner syndrome, Noonan's syndrome, yellow-nail syndrome, intestinal lymphangiectasia, lymphangiomyomatosis and arteriovenous malformations.

Limb swelling may be the presenting and major manifestation of congenital lymphatic malformations, either in a pure form (eg, diffuse lymphangioma) or in combination with a congenital vascular syndrome, such as Klippel-Trénaunay syndrome (varicose veins, excessive long bone growth and vascular birthmark).

Secondary lymphoedema

Secondary lymphoedema results from disruption or obstruction of previously normal lymphatic pathways by other disease processes or as a consequence of surgery or radiotherapy. It is much more common than primary lymphoedema.

Infection

Recurrent episodes of bacterial lymphangitis cause obliteration of the lymphatics and fibrosis of the draining lymph nodes. It is almost always due to streptococci (predominantly beta-haemolytic strains) although *Staphylococcus aureus* and Gram-negative anaerobes have also been implicated. In addition, recurrent lymphangitis is a common complication of lymphoedema. Repeated bouts of cellulitis may also exacerbate the chronic oedema seen in CVI.

Tumour

Malignant cells may obstruct lymphatic vessels, inducing lymphoedema directly or predisposing the patient to bacterial lymphangitis. The most common causes of lower-extremity malignant lymphoedema are prostate cancer in men and lymphoma in women.

Therapy against malignancy may also result in lymphoedema. Oedema of the leg is comparatively common after treatment of pelvic or genital cancer that involves pelvic or inguinal lymph node dissection with or without adjuvant radiotherapy. Cancer itself rarely presents with lymphoedema except in advanced cases presenting late, such as prostate cancer, where venous obstruction may coexist. Relapsed tumour should always be considered in someone with limb swelling after apparent curative cancer treatment.

Postsurgical

Lymph node dissection in the setting of cancer therapy, and vascular surgery, particularly femoral artery endarterectomy or lower-limb bypass surgery, may cause secondary lymphatic obstruction.

Filariasis

A nematode infection, filariasis accounts for the most cases of secondary lymphoedema worldwide. It should be considered in any patient with lymphoedema who has travelled or lived in an endemic area.

Chronic venous insufficiency

Lymphoedema may complicate CVI that has resulted in marked venous hypertension.

Other causes

Other causes associated with obstruction of lymphatic channels include:

- Trauma.
- Tuberculosis.
- Contact dermatitis.
- Rheumatoid arthritis.
- Pregnancy.
- Subcutaneous injections of drugs.

Autoimmune destruction remains a controversial aetiology.

Clinical features

Typical clinical findings include concentric calf oedema with a loss of normal contour, sparing at the level of the ankle joint and significant hind-foot oedema relative to the forefoot, yielding a 'buffalo hump' profile. The toes take on a 'sausage', or 'squared-off', appearance, accompanied by tense oedema.

The unique changes of dermal and subdermal fibrosis (peau d'orange) and Stemmer's sign (an inability of the soft tissues to tent the skin of the interdigital webs) also serve to distinguish lymphoedema from other causes of chronic lower-limb oedema.

Initially there is pitting oedema, which may decrease or disappear with elevation. Increased fluid retention contributes to a sense of heaviness, and early fatigue of the limb is common. The skin retains its normal texture but may appear flushed, and increased skin blood flow will result in an increased temperature of the limb. These features are quite typical of mild disease.

Over a period of years, or with more moderate disease, there is thickening of the skin and the limb may take on a woody (classic peau d'orange) appearance. Pitting is no longer apparent. The oedema may extend more proximally and may not diminish at night with elevation.

Pain is generally absent, but in the presence of lymphangitis the limb may be acutely painful, with a diffuse, superficial burning sensation.

In advanced stages, skin changes are characterised by marked thickening and coarseness. The limb is grossly enlarged, skin creases become enhanced, the limb takes on a mossy, cobblestone appearance with a warty texture (hyperkeratosis) and papillomatosis develops.

Lichenification of the toes develops and intermittent bacterial infection occurs at sites of skin fissures, minor trauma or breakdown induced by interdigital fungal infection. The skin may become broken and the lymph fluid can leak out onto the surface (lymphorrhoea).

Infections in the form of cellulitis, lymphangitis and lymphadenitis are common and ulceration may occur in advanced stages, usually resulting from concomitant venous hypertension. In addition to their inherent danger, infections further damage the lymphatic system. Very rarely, in certain exceptionally severe cases, lymphoedema untreated over many years can lead to a form of cancer known as lymphangiosarcoma.

Lymphoedema manifesting with sudden onset of swelling of one whole leg suggests proximal obstruction, and a search is made for a secondary cause. Pelvic causes of lymphatic obstruction such as tumour must be excluded.

Differential diagnosis

Table 6 lists the differential diagnoses of lymphoedema. CVI and PTS resulting in chronic venous hypertension are most readily confused with lymphoedema. However, the fluid distribution in CVI and PTS is different, being greatest in the ankle area and least over the toes. Chronic venous hypertension is typically associated with:

- Aching discomfort.
- Chronic pruritus.
- Hyperpigmentation.
- Dusky discolouration, with dependency, lipodermatosclerosis and subcutaneous fat necrosis (panniculitis).
- Ulceration (if advanced).

Myxoedema may occur in relation to thyroid dysfunction when abnormal deposits of mucinous material accumulate in the skin. In thyrotoxicosis, the process is focal, whereas in hypothyroidism, myxoedema is more generalised and is accompanied by:

- Roughening of the skin (palms, soles, elbows and knees).
- Brittle nails.
- Dull thinning hair.
- Yellow-orange discolouration of the skin.
- Reduced sweat production.

Lipoedema is the accumulation of fluid and fat deposits under the skin, generally in the legs. It almost exclusively occurs in females and normally appears during puberty or pregnancy. The size of the extremities cannot be reduced by losing weight. The legs may be very tender and ache around the knees. It characteristically spares the feet and does not change the appearance of the skin, which distinguishes it from lymphoedema. People with lipoedema also bruise easily.

Malignancy can cause the appearance or worsening of lymphoedema. There is a tendency for rapid development and relentless progression, and pain may be a feature.

Diagnosis/investigations

In the patient with an oedematous extremity in which lymphoedema is suspected, diagnostic studies are used to establish the diagnosis, assess lymphatic function and document the degree or severity of lymphoedema.

When the physical examination does not conclusively support the diagnosis of lymphoedema (typically in mild cases), additional objective evidence is required to confirm lymphatic dysfunction. Initial investigators relied on lymphangiography but this procedure has now been largely replaced.

Isotopic lymphoscintigraphy

Isotopic lymphoscintigraphy is now the investigation of choice for identifying oedema of lymphatic origin. Radiolabelled colloid or protein is injected into the first web space of each foot and monitored using a gamma camera. Measurement of tracer uptake within the lymph nodes after a defined interval will distinguish lymphoedema from oedema of non-lymphatic origin.

In primary lymphoedema, the channels are obliterated or absent; in 10% they are ectatic and incompetent. In secondary lymphoedema the channels are dilated and the level of obstruction can be determined. In any form of lymphoedema, the appearance of tracer outside the main lymph routes, particularly in the skin (dermal backflow), indicates lymph reflux and suggests proximal progression is delayed. Poor transit of isotope from the injection site suggests hypoplasia of the peripheral lymphatic system.

Direct contrast X-ray lymphography (lymphangiography)

After the lymph vessels have been identified with a vital dye, a contrast medium is administered directly into a peripheral lymphatic vessel. This form of investigation is used rarely.

CT and MRI

Both CT and MRI detect a characteristic 'honeycomb' pattern in the subcutaneous compartment that is not seen with other causes of oedema. In addition, there is the characteristic absence of muscle involvement in lymphoedema. MRI is more informative than CT because it can detect water. CT cannot localise the level of obstruction or differentiate surgically correctable lymphoedema from that which is not. The beneficial aspect of MRI or CT is in determining the cause of secondary lymphoedema.

Table 7: Treatment of lymphoedema

Non-surgical

- Proper skin care — topical emollients
- Manual lymphatic therapy
- Multi-layer, short-stretch bandaging
- Exercise
- Well-fitted compression garments
- Intermittent, multi-compartmental pneumatic compression pump

Surgical

- Lymphatico-venous anastomosis
- Excisional procedures
- Liposuction

Assessing the degree of lymphoedema

The two standard methods for assessing the degree of lymphoedema are measurement of limb circumference and measurement of limb volume displacement. The latter, also known as water displacement volumetry, involves placing the limb in a known volume of water; the volume of water that overflows is measured then converted to mass.

Treatment

Therapy for lymphoedema is best achieved by multiple interrelated strategies (table 7). The goals of therapy are to:

- Reduce limb size.
- Preserve and improve the quality of the skin and subcutaneous tissue.
- Prevent infection.

The most common and accepted treatments for lymphoedema are sequential gradient pump therapy and complete decongestive therapy. Such combination therapy results in the greatest overall reduction in limb volume. Complete decongestive therapy comprises skin care, manual lymphatic drainage, multilayer bandaging, compressive garments and exercise.

Manual lymphatic drainage consists of gentle, rhythmic massaging of the skin to stimulate lymph flow. A typical session will involve drainage of the neck, trunk and involved extremity (in that order).

Compression bandaging involves applying several layers of padding and short-stretch bandages to the involved areas, which, during activity, enhances the pumping action of the lymph vessels, encourages lymphatic flow and softens fluid-swollen areas. Short-stretch bandages are preferred over long-stretch bandages (such as those normally used to treat sprains) to prevent a tourniquet effect.

Regular exercise should always accompany compression bandaging. Dynamic muscle contractions encourage both passive and active drainage.

Compression stockings can be used initially for mild lymphoedema or substituted for bandaging in advanced cases after lymph volume has decreased.

Skin care is an important component of complete decongestive therapy. Gentle cleansing followed by moisturising prevents cracking and fissuring.

Elevating the affected limb lowers venous pressure and therefore filtration, allowing better lymph drainage.

Intermittent biocompression can be accomplished with mechanical pumps, but it is recommended that it be applied at low pressures for no longer than 30-60 minutes. Newer compression pump garments provide compression well into the trunk and/or abdomen and groin areas. Compression pump therapy should always be accompanied by effective manual lymphatic drainage.

Drug treatment

Diuretics are of little benefit in lymphoedema because their main action is to limit capillary filtration. Improvement in patients taking diuretics suggests that the predominant cause of the oedema is not lymphatic.

The benefit of benzopyrones, such as coumarin or flavonoids, that theoretically help remove excess proteins and associated fluid from the tissues remains unproved.

Prevention of infection

Prevention of cellulitis or lymphangitis is crucial to prevent deterioration in oedema. Fungicidal agents between the digits to control tinea pedis, and careful antiseptic dressings after minor wounds, are mandatory.

Bacterial infections should be aggressively treated, often initially with an IV course of broad-spectrum antibiotics followed by more prolonged courses of oral antibiotics. Lifelong prophylaxis may be required in patients with recurrent infections.

Surgery

Surgical therapy is reserved for those few patients who continue to experience unacceptable function despite maximisation of conservative approaches. It comprises excisional or physiological techniques as well as liposuction.

Excisional techniques include:

- Circumferential excision of the lymphoedematous tissue, followed by skin grafting.
- Longitudinal removal of the affected segment of skin and subcutaneous tissue and primary closure.
- Excision of subcutaneous tissue and tunnelling of a dermal flap through the fascia into a muscular compartment of the leg.

Physiological techniques include:

- Lympholymphatic anastomosis (autologous lymphatic grafts to bridge obstructed lymphatic segments).
- Lymphovenous shunt (anastomosis of lymphatic channels to veins).
- Lymphangioplasty with enteromesenteric flap omental transfer (pedicled portion of omentum transposed to the affected limb).

References, further reading and online resources

Available on request from julian.mcallan@reedbusiness.com.au

GP's contribution

DR DAMIEN BRAY
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Case study

WENDY, 64, attends your surgery with a two-week history of a swollen left leg. She is a non-smoker and takes raloxifene for osteoporosis and ramipril for hypertension. Her leg is not painful and has never been very swollen before, although both ankles can get "a bit puffy" in hot weather or with prolonged standing.

Examination reveals moderate pitting oedema to knee level, with loss of calf contour, and more hind-foot swelling compared with ankle swelling. The calf is non-tender, with a flushed appearance of the skin and a circumference 3cm greater than the right.

Questions for the author

What further physical examination should be performed today?

A general physical examination should always be performed. Clinical assessment of general causes focuses on blood pressure and heart rate, cardiovascular examination looking for signs of ventricular (right and/or left) dysfunction and valvular disease. Examination to exclude chronic liver or renal disease as well as thyroid examination should be performed.

It is always important to evaluate the lower-limb pulses (normal arterial circulation will allow compression to be used safely). Local assessment for signs of venous hypertension and varicose veins and for clinical features specific to lymphoedema (involvement of the feet and toes, peau d'orange, inguinal lymphadenopathy) are also indicated.

What are the diagnostic possibilities with Wendy's two-week history of leg oedema?

The finding of a unilateral swollen leg more commonly implicates a local cause such as venous incompetence or venous hypertension. The history of puffy ankles in hot weather or with prolonged standing suggests a degree of venous incompetence. It is also important to exclude a venous thrombotic event, as this is an acute medical emergency.

Lymphoedema would also need to be considered after the above conditions were excluded. Lymphoedema is typically non-pitting (although may be pitting in the early stage) and age precludes a primary cause of lymphoedema.

A secondary obstructive cause typically involves the entire leg.

A subclinical leak or even rupture of a Baker's cyst or a minor calf muscle tear should also be considered.

Uncontrolled systemic hypertension will also promote lower limb swelling, occasionally in an asymmetrical fashion, particularly if there is unilateral venous disease such as varicose veins.

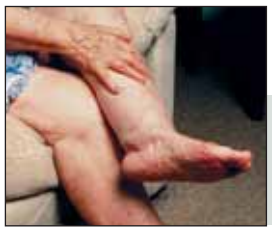
One should also consider general causes such as cardiac dysfunction, liver and renal disease, and thyroid disease.

What investigations should be performed, and in what order?

The initial investigation should be a venous incompetence scan and a venous duplex ultrasound scan to exclude venous incompetence and prior or current deep and/or superficial vein thrombosis, because these conditions are far more common than lymphoedema. Ultrasound will also exclude a Baker's cyst or calf muscle tear.

Blood tests to exclude renal, liver and thyroid disease should also be performed. A protein electrophoretogram is also helpful.

Lymphoedema is best excluded by performing nuclear lymphoscintigraphy. If positive, an abdomino-pelvic CT scan for obstructive causes is the next step.



How to Treat Quiz

Leg oedema — 1 August 2008

INSTRUCTIONS

Complete this quiz online and fill in the GP evaluation form to earn 2 CPD or PDP points. We no longer accept quizzes by post or fax.

The mark required to obtain points is 80%. Please note that some questions have more than one correct answer.

ONLINE ONLY

www.australiandoctor.com.au/cpd/ for immediate feedback

1. Linda, 45, presents with pain and swelling of the left calf for the past few days. She has been in a below-knee cast for a left ankle fracture up until one week ago. Which TWO statements regarding the clinical presentation of DVT are correct?

a) The diagnosis of DVT based on clinical signs and symptoms alone is highly accurate
b) Up to half of patients with acute DVT may lack any specific sign or symptom
c) Signs of DVT include pain with passive plantar-flexion of the foot, known as Homans' sign
d) Many pulmonary emboli may be clinically silent

2. After further history and examination you suspect Linda has a DVT. Which TWO statements about investigating DVT are correct?

a) Duplex ultrasonography is highly accurate in detecting DVT of the iliac veins as well as of the lower-limb veins
b) D-dimer assays are highly specific as well as highly sensitive for DVT
c) The high sensitivity of D-dimer measurements makes it theoretically possible to exclude a DVT on the basis of a negative result, as long as the patient is in a low-risk group
d) Patients with recurrent DVT or DVTs involving more than the tibial vessels should be evaluated for a thrombophilia

3. Duplex ultrasonography confirms that Linda has an isolated calf DVT. Which THREE statements about managing DVT are correct?

a) In the acute DVT setting, lower-limb oedema can be treated with graduated compression stockings and appropriate treatment of the DVT with anticoagulants
b) Accepted anticoagulant therapy for venous thromboembolism is either continuous IV heparin or subcutaneous (SC) enoxaparin, then changing to oral warfarin
c) Patients with proximal thrombosis need IV or SC heparin followed by warfarin for up to six months
d) Indications for vena caval filters include recurrent pulmonary embolism despite adequate anticoagulation

4. Which TWO statements regarding the post-thrombotic syndrome (PTS) are correct?

a) PTS typically occurs within the first two years of the initial episode of DVT
b) Risk factors for PTS appear to include increased BMI
c) PTS typically presents with pain, oedema, hyperpigmentation and/or ulceration
d) Wearing compression stockings long term has not been found to reduce the risk of development of PTS

5. Which THREE statements about chronic venous insufficiency (CVI) are correct?

a) CVI is now thought of as a disease of chronic inflammation
b) When examining the patient with CVI the long and short saphenous veins should be palpated and tested for a cough impulse
c) Investigation of CVI is best performed with venography
d) Raised edges, an irregular appearance, bleeding, and prolonged failure of a venous ulcer to heal raise the suspicion of a malignant ulcer

6. Which TWO statements regarding management of CVI are correct?

a) Compression therapy remains the primary treatment for CVI
b) Diuretics are very helpful in reducing the oedema of CVI
c) Arterial disease should be considered before proceeding with compression therapy for CVI
d) Topical antibiotics are useful in the treatment of venous ulceration to prevent development of infection

7. Dolores, a 55-year-old teacher, consults you regarding long-standing bilateral varicose veins. She is troubled by aching legs and is also concerned about their cosmetic appearance. Which TWO statements regarding superficial venous incompetence are correct?

a) Telangiectatic blemishes and dilated, tortuous, flat, blue-green reticular veins are normal physical findings
b) Reticular veins are defined as permanently dilated, bluish intradermal veins, usually 1mm to <3mm in diameter
c) Varicose veins, while a significant cosmetic issue, do not lead to CVI
d) Deep venous function may be improved by superficial venous surgery

8. Which TWO statements regarding lymphoedema are correct?

a) Primary lymphoedema is much more common than secondary lymphoedema
b) In congenital lymphoedema there is typically aplasia or hypoplasia of lymphatic structures
c) Lymphoedema praecox is most commonly first detected in the third decade of life and is typified by a hyperplasia of the lymphatic vessels
d) In lymphoedema tarda, which typically manifests after age 35-40, the lymphatic channels may be hypoplastic or hyperplastic

9. Which THREE statements about assessing lymphoedema are correct?

a) Typical clinical findings in lymphoedema include concentric calf oedema with a loss of normal contour, significant hind-foot oedema relative to the forefoot and a 'sausage' appearance of the toes
b) Lymphoedema can be confused with oedema due to CVI or PTS; however, the fluid distribution in CVI and PTS is different, being greatest over the ankles and least over the toes
c) In lymphoedema manifesting with sudden onset of swelling of one whole leg, pelvic causes of lymphatic obstruction must be excluded
d) Direct-contrast X-ray lymphography is the investigation of choice for identifying lymphoedema of lymphatic origin

10. Which TWO statements regarding the treatment of lymphoedema are correct?

a) Combination therapy with sequential-gradient pump therapy and complete decongestive therapy results in the greatest overall reduction in limb volume
b) Long-stretch bandages are preferred over short-stretch bandages in compression therapy for lymphoedema
c) Bacterial infections need to be treated aggressively in patients with lymphoedema
d) Benzopyrones, such as coumarin or flavonoids, have been proven to be of benefit in lymphoedema

CPD QUIZ UPDATE

The RACGP now requires that a brief GP evaluation form be completed with every quiz to obtain category 2 CPD or PDP points for the 2008-10 triennium. You can complete this online along with the quiz at **www.australiandoctor.com.au.** Because this is a requirement, we are no longer able to accept the quiz by post or fax. However, we have included the quiz questions here for those who like to prepare the answers before completing the quiz online.

Australian Doctor Education.

HOW TO TREAT Editor: **Dr Wendy Morgan**
Co-ordinator: **Julian McAllan**
Quiz: **Dr Wendy Morgan**

NEXT WEEK Newer, more sensitive tests and recent population-based studies suggest the prevalence of coeliac disease is 10 times more common than previously thought, and 'silent' coeliac disease about seven times more common than symptomatic coeliac disease. With potential sequelae for undiagnosed/untreated disease, including a 20-fold increased risk of solid malignancies and an 80-fold increased risk of intestinal lymphoma, it's time to revisit the diagnosis and management of this condition with next week's How to Treat on this topic. The authors are **Associate Professor Warwick Selby**, senior visiting gastroenterologist, AW Morrow Gastroenterology and Liver Centre, Royal Prince Alfred Hospital, Camperdown, NSW; and clinical associate professor, central clinical school, faculty of medicine, University of Sydney, NSW; and **Dr John Darke**, senior medical registrar and gastroenterology advanced trainee at Hornsby Hospital, Hornsby, NSW.